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Health and Environmental Effects Profile for Nitromethane

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR NITROMETHANE

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16. ABSTRACT

The Health and Environmental Effects Profile for nitromethane was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for nitromethane.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for nitromethane is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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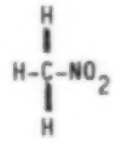
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
FEL	Frank-effect level
GC	Gas chromatography
K_{oc}	Soil adsorption coefficient
K_w	Water-to-air
LC_{Lo}	Lowest lethal concentration
LD_{Lo}	Lowest lethal dose
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MS	Mass spectometry
NOAEL	No-observed-adverse-effect level
OCT	Ornithine carbanyl transferase
ppm	Parts per million
RQ	Reportable Quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
T_4	Serum thyroxin
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Nitromethane is also known as nitrocarbol. The structure and molecular formula for nitromethane are as follows:



Molecular weight: 61.041

Empirical formula: CH_3NO_2

The Chemical Abstract Service (CAS) Registry number is 75-52-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Nitromethane is a colorless liquid with a mild odor at room temperatures. Selected physical properties are listed below [Baker and Bollmeier (1981) unless otherwise noted].

Freezing point:	-28.55°C
Boiling point:	101.20°C
Density	1.138 g/cm³ at 20°C
Refractive Index:	1.38188 at 20°C
Vapor pressure:	
20°C	27.3 mm Hg
25°C	36.7 mm Hg
30°C	46 mm Hg (Verschueren, 1983)
Vapor density: (air = 1.0)	2.11
Evaporation rate: (n-butylacetate = 100)	139
Flash point (open-cup):	44.4°C
Ionization constants:	
K_{nitro}	6.1×10^{-11} at 25°C
K_{acid}	5.6×10^{-4} at 25°C

Water solubility:	
20°C	10.5 wt %
25°C	11.1 wt %
20°C	9.5 mL/100 mL water (Anonymous, 1976)
Log octanol-water partition coefficient:	0.17 (Verschueren, 1983) -0.34 (Valvani et al., 1981)
Conversion factor at 20°C:	1 ppm = 2.50 mg/m³ (Verschueren, 1983)
Log Henry constant (water-nitrogen system, 25°C):	2.9 (Bocek, 1976)

Many organic solvents, including aromatic hydrocarbons, alcohols, esters, ketones, ethers, and carboxylic acids are miscible with nitromethane. It is an excellent solvent for coating materials, waxes, resins, gums and dyes. Nitromethane is resistant to chemical oxidation but can be reduced by various reducing agents to the amine. Prolonged heating results in decomposition (Baker and Bollmeier, 1981).

1.3. PRODUCTION DATA

Nitromethane is produced commercially as a coproduct with nitroethane, 1-nitropropane and 2-nitropropane by reacting nitric acid with excess propane (Baker and Bollmeier, 1981). SRI (1984) lists Angus Chemical Company in Sterlington, LA and the W.R. Grace Company in Deer Park, TX as manufacturers of this chemical as of January, 1984.

Current production figures for nitromethane are not available. In the mid-1960s, nitromethane was being produced in multimillion pound quantities annually (Martin and Baker, 1967). Current use suggests that production is now on the order of ~10 million pounds per year.

1.4. USE DATA

Nitromethane is commercially used as a solvent, as a chemical intermediate for synthesis of pesticides and pharmaceuticals, as a stabilizer for halogenated alkanes and as a fuel (Anonymous, 1976).

As a solvent, nitromethane is used in coatings and inks and as a reaction medium (Baker and Bollmeier, 1981). Addition of small amounts of nitromethane to various chlorinated (1,1,1-trichloroethane) and fluorinated solvents inhibits decomposition and prevents corrosion. Nitromethane is used in specialty propellants and explosives and as a component of racing car fuels.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of nitromethane in water will depend on its ability to undergo chemical, photochemical and biological reactions and partitioning (transport) from the water column into air or sediment. Cundall and Locke (1968) reported that the nitroalkanes (including nitromethane) are not hydrolyzed to any measureable extent by the action of water alone. Anbar and Neta (1967) experimentally determined the rate constant of hydroxyl radical reaction with nitromethane in an aqueous solution of pH 9 to be 1.9×10^{8} M^{-1} sec^{-1}; this translates into a nitromethane half-life of >11 years on the basis of OH• concentration of 10^{-17} M in aquatic media (Mill et al., 1982). Similarly, Dorfman and Adams (1973) reported rate constants in aqueous solutions of pH 9 and pH 10.5 to be 3.1×10^{8} and 8.5×10^{9} M^{-1} sec^{-1}, respectively, which yield half-lives of 7 years and 0.25 years, respectively.

The absorption spectrum of nitromethane in the UV region is a broad continuum extending from 370 nm to a maximum at 198 nm with a weaker maximum at 270 nm (Butler et al. 1983; Kwok et al., 1981). This demonstrates that nitromethane absorbs UV radiation in the environmentally significant range above 290 nm, indicating that photolysis is likely to occur. Unfortunately, data concerning photolysis rates in aqueous solution or under environmental water conditions were not found in the literature searched. Son (1971) studied the flash and continuous photolysis of nitromethane in aqueous solution and demonstrated that the nitromethane decomposed into methane and NO_2. Zeldes and Livingston (1968) reported similar results by photolyzing a basic aqueous solution of nitromethane. Kozubek and Paszyc (1980) and

Marciniak and Paszyc (1980) showed that nitromethane photodecomposes in isopropanol solution and cyclohexane solution, respectively, when irradiated with UV radiation above 290 nm. Data presented in Section 2.2. indicates that nitromethane is photolyzed rapidly in the gas-phase in the atmosphere. It is likely, therefore, that photolysis of nitromethane in the water environment is significant.

Data regarding the microbial degradation of nitromethane in aqueous media (or in soil) are limited. Marion and Malaney (1963) tested the ability of Alcaligenes faecalis, as isolated from activated sludge, to oxidize nitromethane. Nitromethane was found to inhibit A. faecalis growth, which suggests that nitromethane is resistant to oxidation by A. faecalis. In similar tests, Gerhold and Malaney (1966) studied the extent to which nitromethane could be oxidized by activated sludges from waste treatment plants in three Ohio cities. Nitromethane was found to be toxic to two of the activated sludges and only insignificantly oxidized by the third sludge after a long acclimation period. Dhawale and Hornemann (1979) found that crude cell-free extracts from Hansenula mrakii and from nine strains of Streptomyces were able to produce limited amounts of nitrous acid from nitromethane by an oxidative denitrification reaction. Patel et al. (1982) found that methane mono-oxygenase produced by the facultative methane utilizing organism, Methylobacterium sp. (CRL-26), as isolated and enriched from soil samples, was able to oxidize nitromethane. Although the role of microbial degradation of nitromethane in the water environment is not clear, it does not appear to be a significant fate process.

The transport of nitromethane in the aquatic environment will depend on the ability of the compound to volatilize, to adsorb to particulate organic matter or to bioaccumulate in aquatic organisms. Specific experimental data

for these transport mechanisms were not available; however, estimations can be made from the physical properties of nitromethane. The water solubility and vapor pressure of nitromethane can be used to calculate the K_w ratio ($\mu g/cm^3$ of water:$\mu g/cm^3$ of air) from the following equation (Swann et al., 1983):

$$K_w = \frac{(0.0624)\ (\text{water solubility in } (\mu g/cm^3)\ (\text{temp., } °K)}{(\text{Vapor pressure in mm Hg})\ (\text{Molecular weight in g/mol})}$$

Using the water solubility and vapor pressure data at 25°C from Section 1.2., the calculated K_w value for nitromethane is ~870. This means that, at equilibrium, the ratio of nitromethane present in the water to nitromethane present in the air is 870:1.

The K_{oc} and the BCF for nitromethane can be estimated from the water solubility and from equations presented by Kenaga (1980). Because of the high water solubility of nitromethane, it can be predicted that nitromethane is unlikely to be significantly bound to soil and particulate matter in water or to be bioaccumulated in aquatic organisms.

2.2. AIR

Chemicals present in the atmosphere can be removed by either chemical or physical processes. The chemical removal processes include reaction with hydroxyl radicals, reaction with ozone, reaction with other radicals, or photolytic transformations. The physical removal processes include dissolution, adsorption on aerosol particles and dry deposition. Atkinson et al. (1978) calculated the gas-phase rate constant for the initial reaction between hydroxyl radicals and nitromethane to be 1.07×10^{-12} cm^3/mol-sec based upon experimental data generated by Campbell and Goodman (1975).

Using an atmospheric hydroxyl radical concentration of 10^{-6} mol/cm³ (for urban areas; in rural areas, the concentration may be somewhat smaller), the nitromethane half-life based upon reaction with OH radicals can be calculated as follows:

$$t_{1/2} = \frac{0.6931}{1.07 \times 10^{-12} \text{ cm}^3/\text{mol-sec} \times 10^{-6} \text{ mol/cm}^3}$$

This half-life equation yields a value of 7.5 days.

Pitts (1979) reported that the gas-phase reaction between nitromethane and $O(^3P)$ radicals has a rate constant of 3.2×10^{-15} cm³/mol-sec. Considering the concentration of $O(^3P)$ in the atmosphere as 2.5×10^4 molecules cm^{-3} (Graedel, 1978), reaction with $O(^3P)$ radicals is not likely to be significant.

Taylor et al. (1980) calculated atmospheric photodissociation rate coefficients and photodissociation lifetimes for nitromethane as a function of altitude based upon its measured visible and near UV photoabsorption cross-sections at 25°C. Their results are summarized in Table 2-1. At ground level, the photodissociation lifetime of nitromethane was calculated to be 10 hours. Dilling et al. (1976) measured the photodecomposition rate of nitromethane in combination with NO in laboratory tests using simulated atmospheric conditions. Using initial concentrations of 5 ppm of both nitromethane and NO, Dilling et al. (1976) determined that nitromethane had a photodecomposition half-life of 9.2 hours.

In relation to the chemical removal processes, the physical removal processes are not likely to be significant. The data presented for atmospheric nitromethane removal by OH reaction and photodissociation predict that nitromethane will exist in the gas-phase environmentally for relatively short periods of time only.

TABLE 2-1

Variation of Photodissociation Coefficients J and Lifetime 1/J with Altitude for Nitromethane[a,b]

Altitude (km)	J (sec^{-1})	1/J (hours)
0	2.8×10^{-5}	10.0
10	4.0×10^{-5}	6.9
20	4.4×10^{-5}	6.4
30	6.5×10^{-5}	4.3
40	2.7×10^{-4}	1.0
50	5.2×10^{-4}	0.5

[a]Source: Taylor et al., 1980

[b]Calculated from solar flux intensities at a zenith angle of 45°C; a quantum yield of unity was assumed for photodissociation.

2.3. SOIL

The fate and transport of nitromethane in soil has received very little attention in the available literature. The available biodegradation studies have already been discussed in Section 2.1.; from these data, the significance of the microbial degradation of nitromethane in the natural soil environment is not clear.

The photolysis of nitromethane from soil surfaces has not been investigated; however, as noted in Section 2.1., the UV spectra for nitromethane shows considerable absorption in the environmentally significant range above 290 nm. Cundall et al. (1967), Paszyc (1964), and Rebbet and Slagg (1962) reported that liquid nitromethane undergoes photolysis to yield decomposition products including methane and NO_2; however, photolysis rates were not given. It is possible that the photodegradation of nitromethane from soil surfaces may have some environmental significance.

The relatively high vapor pressure and the high evaporation rate of nitromethane (from Section 1.2.) indicate that it may evaporate quite rapidly from dry soil surfaces. Under dry soil conditions, volatilization is likely to be the predominant environmental fate mechanism. In wet soils, this result is not as clear because of the high water solubility of nitromethane.

As noted in Section 2.1., the high water solubility of nitromethane predicts that it will not be bound tightly to soils. Therefore, in many soil types, nitromethane is likely to be leached easily. Experimental adsorption data for soil were not available.

3. EXPOSURE

3.1. WATER

Pertinent data regarding environmental exposure to nitromethane in water were not located in the available literature as cited in the Appendix. The U.S. EPA STORET Data Base reports no listing for nitromethane.

3.2. FOOD

Pellizzari et al. (1982) examined mothers' milk from four urban areas (Bayonne, NJ; Jersey City, NJ; Baton Route, LA; Bridgeville, PA) for organic environmental pollutants. Nitromethane was detected in one of the eight samples examined.

3.3. INHALATION

Nitromethane has been detected in gaseous emissions from automobiles (Hurn et al., 1974), in tobacco smoke and in turbine emissions (Graedel, 1978). It has also been detected as an air pollutant emission from high explosive production at government-owned, contractor-operated ammunition plants (Thompson et al., 1979). At these ammunition plants, nitromethane is produced as a volatile by-product during the formation of RDX explosive from hexamethylenetetramine.

3.4. DERMAL

Pertinent data regarding environmental dermal exposure to nitromethane were not located in the available literature as cited in the Appendix.

4. PHARMACOKINETICS

4.1. ABSORPTION

Machle et al. (1940) reported toxic effects when nitromethane was administered orally or by inhalation. No illness resulted from dermal application of nitromethane. These data imply that absorption follows oral or inhalation exposure to nitromethane. Quantitative data regarding absorption of nitromethane were not located in the available literature.

4.2. DISTRIBUTION

Pertinent data regarding the distribution of nitromethane were not located in the available literature as cited in the Appendix.

4.3. METABOLISM

When a liver microsomal preparation from phenobarbital-pretreated rats was incubated aerobically with nitromethane and NADPH, the stoichiometric formation of nitrite and formaldehyde was observed (Sakurai et al., 1980). Addition of nitromethane to liver microsomes under anaerobic conditions resulted in the continuous linear formation of formaldehyde but not nitrite. A peak at 437 nm was seen in the difference spectrum of oxidized P-450, which was interpreted as the formation of a cytochrome P-450-NO complex.

Within 3 minutes of the addition of 0.04 M nitromethane to a reduced myoglobin solution at pH 7.4, the visible spectrum of the solution shifts to show the complete formation of a complex that absorbs at 425 nm (Mansuy et al., 1977a). Nitromethane and human hemoglobin under similar conditions form a complex that absorbs at 421 nm. Nitromethane forms a similar complex with cytochrome P-450 (Mansuy et al., 1977b).

Wade et al. (1977) proposed that three binding sites for nitromethane exist on cyctochrome P-450 isolated from rabbit hepatic microsomes. Nitromethane appears to compete with carbon monoxide for a common binding site.

Rats given single or repeated intraperitoneal injections of nitromethane (0.11-1.5 g/kg) did not appear to produce methemoglobin (Dequidt et al., 1973). Traces of methemoglobin were seen in animals exposed to nitromethane in the atmosphere (up to 13,000 ppm, unspecified time period).

Nitromethane incubated with rat microsomes under oxidative conditions yielded 0.24 ppm nitrite (Marletta and Stuehr, 1983).

4.4. EXCRETION

Nitromethane has been detected in pooled urine samples from normal untreated mice (Miyashita and Robinson, 1980). Daytime urine was collected from male Swiss Webster mice for a 40-day period and subjected to analysis by GC and MS.

In a study that tested 12 women in New Jersey, Pennsylvania and Louisiana, nitromethane was found in one sample of human milk (Pellizzari et al., 1982).

5. EFFECTS

5.1. CARCINOGENICITY

According to Lewis et al. (1979), histopathologic examinations of liver, kidney, thyroid, brain, lungs and trachea of rats and rabbits exposed to nitromethane in air (98 ppm or 745 ppm for 6 months) revealed no neoplasms. No other pertinent data regarding the carcinogenicity of nitromethane were found in the available literature.

5.2. MUTAGENICITY

Gocke et al. (1981) conducted a series of mutagenicity screening tests on 31 compounds, one of which was nitromethane. In the Ames assay, five dose levels of nitromethane were each tested in five different tester strains of Salmonella typhimurium with and without metabolic activation. The Basc test on Drosophila melanogaster (one dose, unspecified) was also performed, as was the micronucleus test in mice (doses unspecified). Nitromethane was not found to be mutagenic in any of the assays employed, although no data were provided in the report.

Other studies with S. typhimurium also failed to detect any mutagenic activity of nitromethane (Chiu et al., 1978; Lofroth et al., 1981).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of nitromethane were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Female Charles River albino rats were injected intraperitoneally with 0.5 mL of 1.5 M nitromethane in 0.9% NaCl every third day (Whitman et al., 1977). The injections began 1 week before the rats were bred and continued throughout gestation. It is not specifically stated whether treatments also continued throughout lactation. No differences were observed between treated animals and controls with respect to percentages of successful matings,

litter size, death rates of pups, birth weights or mothering behavior. At 2.5 months of age, the pups were subjected to behavioral testing in a maze-learning apparatus. The offspring of treated rats clearly showed impaired maze learning when compared with controls ($p<0.05$).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of nitromethane were not located in the available literature. Subchronic studies have been performed.

Lewis et al. (1979) exposed male Sprague-Dawley rats and male New Zealand white rabbits to technical grade (96.5% pure) nitromethane in air 7 hours/day, 5 days/week for 6 months. Two exposure concentrations were employed (98 ppm and 745 ppm). Rats were sacrificed at 2 days, 10 days and 1, 3 and 6 months of exposure (10 rats/group); rabbits were sacrificed at 1, 3 and 6 months (5 animals/group). Physiologic, serum biochemical and histopathologic evaluations were conducted.

Weight gain in rats exposed to 745 ppm nitromethane was significantly decreased compared with controls (significance level not stated) (Lewis et al., 1979). The growth rate in rabbits did not appear to be affected by treatment. Rat hematocrits were decreased at the highest exposure level for all except those sacrificed at the 2-day interval ($p<0.01$). Rat hemoglobins were also depressed at this exposure level for these same intervals ($p<0.005$). Hematologic parameters in rabbits were not affected significantly except for a transient depression in hemoglobin concentration seen at both exposure levels after 1 month. The erythrocyte count, methemoglobin concentrations and prothrombin times were not affected in either species.

Serum OCT, SGPT, and T_4 levels in rats were comparable with controls (Lewis et al., 1979). In rabbits, elevated OCT levels ($p<0.05$) were seen at both nitromethane concentrations after 1 and 3 months of exposure. After 6

months, serum OCT levels were lower than control values. Rabbits exposed to 745 ppm had depressed T_4 levels by 1 month ($p<0.05$). T_4 levels in rabbits exposed to 98 ppm were depressed by 6 months ($p<0.05$). SGPT levels were not affected in rabbits at either nitromethane concentration.

Elevated thyroid weights were seen in rats (745 ppm) and rabbits (98 and 745 ppm) after 6 months of exposure to nitromethane (Lewis et al., 1979). Rats also had consistently smaller lung weights at all sampling intervals; however, this observation was not statistically significant. Hemorrhage, necrosis and congestion of alveolar and alveolar duct walls were observed in the lungs of rabbits at both nitromethane concentrations by the 1-month interval. No histopathologic abnormalities were seen in rats exposed up to 6 months.

Young male albino rats (10 per group) were given nitromethane in their drinking water (0.25% and 0.1%) for 15 weeks (Weatherby, 1955). Histopathological examination was performed on major organs of rats surviving to termination. Animals that died during the test were cannibalized, hence, not examined. Granular hepatocellular degeneration was seen in 6 of 7 survivors of the 0.25% concentration level. Two of these animals also exhibited mild changes in the spleen. Two of six survivors in the 0.1% group and 1 of 10 control animals exhibited large hepatic cells with prominent nuclei. In both groups, all other organs appeared normal. Weight gain in the two treated groups was slower than in controls. Water consumption was decreased in both treated groups relative to controls. Intake of the chemical, estimated from data provided by the author, was ~80 mg/kg/day in the low dose group and ~150 mg/kg/day in the high dose group.

5.6. OTHER RELEVANT INFORMATION

The TLV-TWA for nitromethane has been set at 100 ppm (ACGIH, 1983; NIOSH, 1974). The air odor threshold (as the geometric average of all available literature data) has been determined to be 3.5 ppm (Amoore and Hautala, 1983).

The acute effects of nitromethane seen by different experiments in a number of species are presented in Table 5-1.

Machle et al. (1940) found that the oral LD_{50} in rabbits was 750-1000 mg/kg. Progressive weakness and collapse, incoordination leading to ataxia and changes in respiration were noted beginning 20-40 minutes after administration. No methemoglobin formation was noted.

Weatherby (1955) administered nitromethane orally to dogs (125, 250, 500, 1000 and 1500 mg/kg). All animals except those receiving 125 mg/kg either died within ~30 hours or were killed in a moribund condition. Tissues were prepared for microscopic study from animals at all dose levels. The severity of lesions seen on the liver appeared to be dose related. Kidney damage was seen only at the highest dose. Similar histopathology was seen in dogs receiving nitromethane intravenously.

Inhalation experiments with rabbits and guinea pigs were performed by Machle et al. (1940). Monkeys were also used at low concentrations. At concentrations of nitromethane in air of $\geq$0.1%, mortality was related to the total dose received (calculated as the exposure concentration times the duration). Rabbits and guinea pigs (2/species/exposure) showed 100% mortality at 1% nitromethane for 6 hours, 3% for 2 hours and 5% for 1 hour. No mortality was seen at 1% for 1 hour or 3% for 15 minutes. Less than 100% mortality was seen at intermediate concentrations and durations. Guinea pigs seemed somewhat more susceptible than rabbits.

TABLE 5-1

Acute Effects of Nitromethane

Animal	Route	LD_{50} (mg/kg)	Reference
Dog	oral	125-250	Weatherby, 1955
Dog	subcutaneous	565-1130	Gibbs and Reichert, 1891
Dog	intravenous	800 (LD_{Lo})	Weatherby, 1955
Rat	oral	1210 ± 322	Martin and Baker, 1967
Rabbit	intravenous	750-1000	Weatherby, 1955
Rabbit	oral	750-1000	Machle et al., 1940
Mouse	oral	1440 ± 110	Weatherby, 1955
Monkey	inhalation	1000 ppm (LC_{Lo})	Machle et al., 1940

Machle et al. (1940) observed a latent period before the onset of symptoms, which varied inversely with the concentration of nitromethane. The symptoms of poisoning following inhalation were similar in all three species used. Animals first appeared restless and exhibited a slight irritation of the respiratory tract. After the latent period the animals appeared ill and slightly narcotized. Salivation, weakness, ataxia and lack of coordination were noted as the exposure continued. Convulsions, twitching and cerebellar fits were often seen. Hemoglobin percentage and erythroycte count were lower in exposed animals but these changes were not significant when compared with controls.

Histidase activity in rat liver was decreased by 80% when an unspecified dose of nitromethane was administered subcutaneously for 18 days (Wang and Lee, 1973). No significant alteration of amino acid patterns except histidine were found in either liver or blood plasma. Histidine concentrations, however, reached a steady-state level of 3-4 times the concentration in controls after 6 days of injection.

Inbred weanling male Sprague-Dawley rats received subcutaneous injections of nitromethane (1.2 M, 0.4 mℓ/100 g bw) (Lee and Wang, 1975). Hepatic histidase activity showed a 40% decrease 2 hours after a single injection. Twenty-four and 48 hours after injection, the activity had decreased 60-70%. Eighty-four hours after injection, histidase activity had recovered. When rats were injected every other day for up to 18 days, histidase activity had decreased by 80% on the 18th day. After 18 days the histidine concentrations in plasma, brain, liver and kidney were found to be increased 4.7, 2.7, 3.0 and 1.7 times (respectively) when compared with control values. Histidine concentrations in urine samples of treated animals were elevated significantly in comparison with controls. Treatment

with nitromethane appears to produce a condition that mimics the human inborn error of metabolism, histidinemia, in which histidase activity is deficient and high levels of histidine are seen in the plasma and tissues. Mental retardation is also seen in ~40% of affected children.

The relative weights of liver, kidney or brain in nitromethane-treated animals were not significantly different from controls (Lee and Wang, 1975). The liver protein content also was not influenced by the treatment.

6. AQUATIC TOXICITY

6.1. ACUTE

Curtis et al. (1980) reported that nitromethane concentrations of 659.2 ppm (nominal) were not lethal to fathead minnows, Pimephales promelas, over a 96-hour exposure, although "severe sublethal effects" were observed.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of nitromethane were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Pertinent data regarding the effect of nitromethane to plants were not located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding the effect of residues of nitromethane were not located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

The current occupational exposure standards recommended by the ACGIH (1983) and NIOSH (1974) are a TLV-TWA of 100 ppm (250 mg/m³) and a TLV-STEL of 150 ppm (375 mg/m³). West Germany also recommends 100 ppm, the USSR suggests 9 ppm, and Romania suggests 30 ppm (ACGIH, 1980).

8. RISK ASSESSMENT

Data are inadequate to assess the potential carcinogenicity and mutagenicity of nitromethane.

In an inhalation study, Lewis et al. (1979) exposed male Sprague-Dawley rats and male New Zealand white rabbits to two concentrations of nitromethane (98 ppm and 745 ppm, 7 hours/day, 5 days/week for 6 months). Rats exposed to 98 ppm nitromethane showed no significant differences (in comparison with controls) in growth rate, hematocrit, hemoglobin concentration, serum biochemical evaluations, organ weights and histopathology of a variety of organs.

Rabbits exposed to the same concentration of nitromethane (98 ppm) exhibited statistically significant differences in serum T_4 levels, serum OCT levels and thyroid weights (Lewis et al., 1979). After 1 month of exposure, hemorrhage, congestion and some necrosis were observed in alveolar and alveolar duct walls in rabbit lungs.

While it is possible that this concentration of nitromethane (98 ppm) corresponds to a NOAEL in rats, it does not in rabbits, since adverse effects were observed at this level. Insufficient toxicological observations and dosing regimen for nitromethane in this study precludes derivation of an ADI.

In another subchronic study by Weatherby (1955), nitromethane was administered to young male rats at 0.25% or 0.1% in their drinking water for 15 weeks. At the higher concentration, there were 3/10 unexplained deaths. Of the 7 survivors, 6 had lesions in the liver and spleen upon histological examination of these organs. At 0.1% there were 4/10 unexplained deaths. Histological examinations of the survivors showed no significant differences

from controls. There were no deaths in the control group. It is impossible to determine if the observed deaths in the experimental groups were treatment-related.

The data from two subchronic studies (Lewis et al., 1979; Weatherby, 1955) are judged to be an inadequate basis for the derivation of an ADI for nitromethane. No other subchronic studies were encountered in the available literature.

9. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

9.1. ORAL

Adequate chronic or subchronic studies were not available for the derivation of an oral RQ. The only subchronic oral study available was performed by Weatherby (1955). Nitromethane was administered to rats in their drinking water for 15 weeks (0.25% and 0.1%). There were no deaths in the control group, but 3/10 animals died in the 0.25% group and 4/10 died in the 0.1% group. No cause of death was determined because the animals were destroyed by their cage mates. Because of these unexplained deaths, the data from this experiment are judged inadequate for the derivation of an oral RQ.

9.2. INHALATION

No chronic studies on the inhalation of nitromethane were available. A subchronic study was performed by Lewis et al. (1979). Male Sprague-Dawley rats and male New Zealand white rabbits were exposed to two concentrations of nitromethane (98 or 745 ppm, corresponding to 244.2 and 1856.1 mg/m^3, respectively) for 7 hours/day, 5 days/week for up to 6 months. Changes in hematology, serum biochemistry, organ weights and the histopathology of various organs were monitored.

The CSs calculated from this experiment for nitromethane are summarized in Table 9-1; both CSs were associated with RQs of 1000.

Rats exposed to 1856.1 mg/m^3 of nitromethane were observed to have significantly increased thyroid weights when compared with controls ($p<0.001$) (Lewis et al., 1979). Rat hematocrits ($p<0.01$) and hemoglobin concentrations ($p<0.005$) were depressed. There were no significant changes in serum biochemical or histopathologic parameters.

TABLE 9-1

Composite Scores for Nitromethane[a]

Species	Route	Concentration in Air (ppm)	Human MED[b] (mg/day)	RV_d	Effect	RV_e	CS	RQ
Rat	inhalation	745 for ≤6 months	296.4	1.75	Increased thyroid weights	4	7.0	1000
Rabbit	inhalation	98 for ≤6 months	127.5	2.35	Increased thyroid weights; pulmonary necrosis, hemorrhage and congestion	6	14.1	1000

[a]Source: Lewis et al., 1979

[b]A safety factor of 10 was applied to estimate a chronic value.

A transient decrease in hemoglobin concentration was seen in rabbits after 1 month of exposure to 244.2 mg/m³ nitromethane (Lewis et al., 1979). T_4 levels were reduced ($p<0.05$) and OCT levels were first elevated (1- and 3-month intervals) and then reduced (6-month interval) ($p<0.05$). Thyroid weights were increased in comparison with controls (significance not stated). Upon histological examination, hemorrhage, congestion and necrosis were seen in alveolar and alveolar duct walls of exposed rabbits. The CSs calculated from this experiment for nitromethane are summarized in Table 9-1; both CSs were associated with RQs of 1000.

The highest CS is associated with the data for rabbits exposed to 244.2 mg/m³ nitromethane 7 hours/day, 5 days/week for 6 months. The equivalent human MED is derived by expanding the exposure from 7-24 hours/day and 5-7 days/week and by applying rabbit body weight/human body weight and breathing rate correction factors and by multiplying assumed human body weight (70 kg). A human MED of 127.5 mg/day is calculated by dividing 1274.8 by 10 to estimate a chronic exposure level. This corresponds to an RV_d of 2.35. The effect of necrosis in alveolar and alveolar duct walls gives an RV_e of 6. The CS, calculated as the product of RV_d and RV_e, is 14.1, which is associated with an RQ of 1000. This CS is chosen to represent the toxicity of nitromethane (Table 9-2).

TABLE 9-2

NITROMETHANE

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*	127.5 mg/day
Effect:	pulmonary congestion, hemorrhage, necrosis
Reference:	Lewis et al., 1979
RV_d:	2.35
RV_e:	6
Composite score:	14.1
RQ:	1000

*Equivalent human dose

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

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